ANAESTHETIC STEROID COMPOSITIONS

Lodged (23) 16th December, 1971
Accepted (44) 18th May, 1976
Published (41) 21st June, 1973

Invention Priority (30) 17th December, 1970 Great Britain 60068/70

Applicant (71) GLAXO LABORATORIES LIMITED

Actual Inventor (72) GORDON HANLEY PHILLIPPS and BENJAMIN DAVIS

Related Art (56) 463183 (47894/72) 87.16, 09.12
36962/72 09.16, 87.16
36959/71 87.16

The following statement is a full description of this invention, including the best method of performing it known

F. D. Atkinson, Government Printer, Canberra
This invention is concerned with improvements in or relating to pharmaceutical preparations having anaesthetic activity, and more particularly preparations suitable for intravenous injection.

It has long been known that a number of steroids give rise to profound depression of the central nervous system and act pharmacodynamically as anaesthetics or hypnotics. Such compounds have been the subject of considerable study in an attempt to find anaesthetics to replace such substances as thiopentone sodium normally used but well known to be accompanied by some degree of hazard or disadvantage. The literature shows that very many steroid compounds have been studied in this regard. Reviews and discussions of some of the work carried out are to be found, for example, in "Methods in Hormone Research" (Edited by Ralph I. Dorfman, Vol. III, Part A, Academic Press London and New York 1964, pages 415-475); H. Witzel, Z. Vitamin Hormone-Fermentforsch 1959, 10, 46-74; H. Selye, Endocrinology, 1942, 30, 437-453; and S.K. Figdor et al, J. Pharmacol. Exptl, Therap., 1957, 119, 299-309.

A thorough review of the literature indicates that anaesthetic steroids generally possess poor activity and/or long induction periods. With such compounds a variety of undesired side effects such as paraesthesia and vein damage have been noted. Many steroid compounds having anaesthetic
tion are also of poor solubility and thus much research hitherto been directed to the introduction of solubilising groups into such steroids, e.g. by the formation of partial esters with di- or polybasic acids; such work has hitherto not resulted in the discovery of a satisfactory anaesthetic steroid compound. Anaesthetic steroids are generally relatively simple pregnane derivatives, often hydroxylated in the 3-position, the general trend having been in the latter case to study 3β-hydroxy compounds in preference to 3α-hydroxy compounds.

In our Application No. 16454/70 (459624) (Case 5) we have described anaesthetic compositions containing as principal anaesthetic component 3α-hydroxy-5α-pregnane-1,20-dione. As stated in our said Application this substance has quite remarkable properties as an anaesthetic and the compositions of our said Application thus induce anaesthesia and possess short induction periods, the anaesthetic action at suitable doses being indeed instantaneous;
the solutions are thus excellent anaesthetics for inducing anaesthesia in human and veterinary medicine, which is to be maintained e.g. by an inhalation anaesthetic such as ether, halothane, nitrous oxide and trichlorethylene. The solutions are however capable of maintaining anaesthesia and analgesia to a sufficient degree to enable various surgical operations to be conducted without the aid of an inhalation anaesthetic, the required degree of anaesthesia being maintained if necessary by repeated administration (or even continuous administration).

Recovery from anaesthesia (where this is induced only by the solutions of our said prior Application) is excellent, the patient exhibiting a feeling of well-being in distinction to the unpleasant after effects generally associated with conventional anaesthetics. Moreover, the aforesaid anaesthetic solutions in general give rise to none of the undesired side-effects previously associated with steroidal anaesthetics.

The compositions of our said prior Application are aqueous solutions containing 3α-hydroxy-5α pregmane-11,20 dione.

In our prior patent No. 463,183 the steroid and surfactants used to prepare the solutions are the same as those used in the present application to prepare suspensions but the amount of surfactant used to produce a solution or suspension containing the same concentration of 3α-hydroxy-5α-pregnane-11,20 dione will however be different. Thus in preparing the solutions of the prior patent it is necessary to use at least 5% by
weight and advantageously above 10% by weight of surfactant. A very convenient proportion of surfactant is said to be 20% by weight. In order to prepare the suspensions of the present application it is necessary to use 0.5% to 5% by weight by surfactant.

In our copending application No. 36,959/71 there is disclosed and claimed compositions containing active steroids in solution in an organic medium whereas in the present application the active steroid is in suspension as fine solid particles. In accordance with this invention we have found that anaesthetic compositions
may be prepared in the form of sterile aqueous suspensions for injecting comprising the said anaesthetic steroid \(3\alpha\)-hydroxy-5\(\alpha\)-pregnane-11,20-dione as active ingredient together with from 0.5\% to 5\% by weight of a parentally acceptable surface active agent.

Thus aqueous suspensions may be prepared which are suitable for administration by intravenous injection and possess the desirable anaesthetic properties of the composition described in our said prior Application. Although in the compositions of this invention the steroid anaesthetic is in solid form it appears that upon intravenous injection the steroid passes rapidly into solution in the blood.

The compositions according to the invention are prepared in generally conventional manner. Thus the compositions contain a parenterally acceptable surface active component to assist dispersion of the active steroid and to prevent agglomeration of the particles. The surface active component must naturally be one which is physiologically compatible in the species it is intended to treat (man or animal), i.e. it should of itself give rise to no physiologically unacceptable side effects in the dosages employed.

Non-ionic surface active agents are generally suitable for this purpose. The suspensions in accordance with the invention preferably contain (as surface active component) one or more non-ionic surfactants, the HLB value (or resultant HLB value of the surface active component) being preferably at least 9; generally the HLB value will be below 15.
Where more than one surfactant is present the HLB value of an individual surfactant is preferably not greater than 30.

Particularly useful surfactants are those carrying a polyoxyethylene grouping chosen, for example from the following classes:- Polyoxyethylated derivatives of fatty (C12-C20) glyceride oils, e.g. castor oil, preferably containing from at least 35 (e.g. from 35 to 45 or 60 or more) oxyethylene groups, per mole of fatty oil. Polyoxyethylene ethers (containing from 10 to 30 oxyethylene groups) of long chain alcohols (containing for example from 12-18 carbon atoms, e.g. dodecanol).

Polyoxyethylene-polyoxypropylene ethers preferably containing from 5-160 (e.g. 15 to 150) and from 15 to 50 oxyethylene and oxypropylene groups respectively. Polyoxyethylene ethers (containing from 6 to 12 oxyethylene groups) of alkyl phenols the alkyl groups of which preferably contain 6-10 carbon atoms.

Polyoxyethylated (preferably containing from 15 to 30 oxyethylene groups) fatty acid (e.g. C12-18) esters of sugar alcohol anhydrides e.g. sorbitan or mannitan.

Polyethylene glycol esters (preferably containing from 6 to 40 ethylene oxide units) of long chain fatty acids (containing for example 12-18 C atoms) e.g. polyethyleneglycol mono-oleate (preferably containing for example 8 ethylene oxide units).

Long-chain (e.g. C10-16) alkanoyl mono- and di-alkanolamides (the alkanol portions of which for example
contain 1-5 C atoms) for example lauroyl mono- and di-ethanolamides are also useful.

Other useful surfactants include phospholipids such as lecithins e.g. egg or soyabean lecithins.

Examples of non-ionic surface active agents, of the foregoing types, particularly useful in accordance with the invention include:

Cremophor EL, a polyoxyethylated castor oil containing about 40 ethylene oxide units per triglyceride unit;

Tween 80, polyoxyethylene sorbitan mono-oleate containing about 20 ethylene oxide units;

Tween 60, polyoxyethylene sorbitan monostearate containing about 20 ethylene oxide units;

Tween 40, polyoxyethylene sorbitan monopalmitate containing about 20 ethylene oxide units;

Pluronic F68, a block copolymer of ethylene oxide and propylene oxide containing about 150 ethylene oxide units and about 40 propylene oxide units; and

Brij 35, polyoxyethylene dodecyl ether containing about 23 ethylene oxide units.

The words Cremophor, Tween, Pluronic and Brij are registered trade marks.

The compositions according to the invention further desirably contain a parenterally acceptable suspending agent to assist in maintaining the steroid in suspension. Suspending agents which may be used include parenterally acceptable hydrophilic colloids such as dextran, preferably a dextran
having an average molecular weight of from 15,000 to 70,000.

Various other types of suspending agents useful in the preparation of injectable pharmaceutical compositions are well known and may be used in the compositions in this invention, for example, polyvinylpyrrolidone, polyvinyl alcohol, sorbitol, mannitol, a polyoxyethylene glycol, carboxymethylcellulose, colloidal silica and colloidal silicates.

The compositions according to the invention may if desired contain an antifoam agent, for example, a parenterally acceptable silicone antifoam agent, e.g. dimethyl polysiloxane.

The composition may further include one or more parenterally acceptable, water-soluble substances serving to render the compositions approximately isotonic with blood, suitable substances for this purpose being dextrose or glycerol.

The anaesthetic steroid active ingredient in the composition in accordance with this invention is preferably of very fine particle size, particle sizes below 5µm (average particle size) being preferred. Advantageously the average particle size of the steroid should be below 2µm. The suspensions preferably contain 0.1 to 2.0% by weight of the composition of the active steroid.

It is particularly convenient to prepare the aforesaid steroid anaesthetic substance in small particle form by rapid precipitation from solution in a suitable solvent. Thus for example the steroid may be dissolved in a solvent such as dimethylformamide, dimethylacetamide or tetrahydro-
furan and the solution added to water preferably containing a surface active agent (for example of the aforementioned types) with agitation, for example with a high speed stirrer. The precipitation is preferably effected at low temperature to promote formation of fine particles, e.g. at 5°C. Other methods of producing small size crystal material from solution are well known to those skilled in the art.

In general the composition according to the invention will contain at least 0.5% and usually 0.5 - 5.0% (by weight) of surface active component. The proportion of suspending agent, where used, may be from 0.1 - 10% by weight.

Where an antifoam substance is included this will generally be present in quite small proportions, for example of the order of from 50 to 150 p.p.m by weight.

The compositions according to the invention are preferably presented in dosage unit form i.e. in containers for example ampoules or vials, each such container containing from 10 mg to 300 mg of the aforesaid anaesthetic steroid. While the dose to be given to any particular patient will, as is known in the anaesthetic art, depend upon the physical condition of the patient and the degree and period of anaesthesia required, dosage units having a content of active ingredient within the range just mentioned will be found to provide the anaesthetist with a convenient quantity of anaesthetic in a single unit from which the particular dose required for a given patient may readily be taken.
Compositions in accordance with the invention may take the form of a 'two-pack' composition comprising a first container containing the steroid and a second container containing the liquid suspension vehicle, the contents of the two containers being intended for admixture by an anaesthetist, for example just prior to use.

Compositions according to the invention may be presented in the form of powders, e.g. wettable powders adapted to be readily dispersed in sterile water for injection, for example just prior to administration. Such wettable powders may be prepared using the same ingredients as in the preparation of suspensions, the various components being selected, in conventional manner, to provide a readily dispersable product. Preferably, the wettable powders comprise a freeze dried mixture of the active steroid and the surface active component. Such wettable powders represent a convenient means of presentation of the first component of the 'two-pack' composition above referred to.

The compositions of the invention may of course be presented in combination with printed directions for their use as anaesthetics in medicine for parenteral administration.

For a better understanding of the invention the following Examples are given only as illustrations.

**Example 1 Aqueous Suspension**

5 ml of a 20% solution of 3α-hydroxy-5α-pregnane-11,20-dione in dimethyl formamide at 60°C were added to
95 ml of a 2.5\% by weight Cremophor EL solution of 50\C while agitating with a high speed stirrer. The precipitate was washed by centrifugal decantation and a 1\% (by weight) suspension prepared in an aqueous medium containing by weight 1\% Cremophor EL, 5\% dextrose, 6\% dextran (MW, 40,000) 100 p.p.m. silicone antifoam.

**Example 2 Aqueous Suspension**

A precipitate of 3α-hydroxy-5α-pregnane-11,20-dione prepared as in Example 1 was formulated as a 1\% by weight suspension in an aqueous medium containing by weight 1\% Cremophor EL, 0.9\% polyvinylpyrrolidone and 100 p.p.m. of silicone antifoam.

**Example 3**

0.2 g of 3α-hydroxy-5α-pregnane-11,20-dione finely ground in a fluid-energy mill, and 0.02 g of Pluronic F68 were made into a thick slurry with distilled water and ball-milled in a small agate mill for 15 minutes and freeze-dried. The freeze-dried solid may be readily re-dispersed to give a 1\% by weight suspension in a solution containing (by weight) 0.2\% Pluronic F68, 5\% dextrose and 100 p.p.m. of silicone antifoam.

**Example 4**

To 2.5\% by weight Tween 80 at 50\C, 5mml of a 20\% by weight solution of 3α-hydroxy-5α-pregnane-11,20-dione in dimethylformamide at 60\C were added. The precipitated steroid was freeze-dried and could be re-dispersed to give a 1\% by weight suspension by a solution containing 1\% by weight Cremophor EL,
1% by weight dextran (MW 20,000) and 100 p.p.m. silicone antifoam.
THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A composition adapted for use in medicine as an anaesthetic by parenteral administration comprising 3α-hydroxy-5α-pregnane-11,20-dione as active ingredient as a suspension of fine particles in a liquid aqueous suspension medium, and from 0.5% to 5% by weight of a parenterally acceptable surface active component, said suspension not being optically clear.

2. A composition as claimed in claim 1 wherein the active ingredient has an average particle size of less than 5 µm.

3. A composition as claimed in claim 1 or claim 2 wherein the surface active component has an HLB value of at least 9.

4. A composition as claimed in any of claims 1 to 3 in which the surface active component has an HLB value of not more than 15.

5. A composition as claimed in anyone of claims 1 to 4 wherein the surface active component comprises polyoxyethylated derivative of a fatty glyceride oil, having 12-20 carbon atoms, and containing at least 35 oxyethylene groups per mole of fatty oil; a polyoxyethylene ether of an alcohol having 12-18 carbon atoms and containing 10 - 30 oxyethylene groups; a polyoxyethylene-polyoxypropylene ether containing 5-160 oxyethylene groups and 15-50 oxypropylene groups; a poly-
oxyethylated fatty acid (having 12-18 carbon atoms) ester of sorbitan or mannitan containing 15-30 oxyethylene groups; a polyethylene glycol ester of a fatty acid having 12-18 carbon atoms, and containing 6-40 oxyethylene groups; or a phospholipid.

6. A composition as claimed in any one of the preceding claims also containing a parenterally acceptable suspending agent.

7. A composition as claimed in claim 7 wherein the suspending agent is a hydrophilic colloid, polyvinylpyrrolidone, polyvinyl alcohol, sorbitol, mannitol, a polyoxyethylene glycol, carboxymethylcellulose, colloidal silica or a colloidal silicate.

8. A composition as claimed in claim 7 wherein the suspending agent is a dextran having an average molecular weight of 15,000 to 70,000.

9. A composition as claimed in any one of claims 7 to 9 wherein the suspending agent is present in an amount of from 0.1 - 10% by weight of the composition.

10. A composition as claimed in any one of the preceding claims also containing an anti-foam agent.

11. A composition as claimed in claim 10 wherein the antifoam agent is dimethyl polysiloxane.

12. A composition as claimed in claim 10 or claim 11 wherein the antifoam agent is present in an amount of 50 to 150 p.p.m.
13. A composition as claimed in any one of the preceding claims which is isotonic with blood.

14. A composition as claimed in any one of the preceding claims wherein the active ingredient is present in an amount of 0.1 to 2.0% by weight of the composition.

15. A composition as claimed in any one of the preceding claims in dosage unit form each dosage unit containing 10 to 300 mg of 3α-hydroxy-5α-pregnane-11,20-dione.

16. A composition in the form of a wettable powder, for dispersion in sterile water to provide a composition as claimed in any of the preceding claims, said wettable powder comprising 3α-hydroxy-5α-pregnane-11,20-dione and a parenterally acceptable surface active agent.

17. A composition as claimed in claim 16 comprising a freeze-dried mixture of the active ingredient and the surface active agent.

18. An anaesthetic composition adapted for use as an anaesthetic in medium substantially as described with reference to the Examples.

19. A two-pack composition for use as an anaesthetic in medicine comprising a first container containing a wettable powder comprising 3α-hydroxy-5α-pregnane-11,20-dione and a parenterally acceptable surface active agent and a second container containing a sterile injectable aqueous suspension medium for said 3α-hydroxy-5α-pregnane-11,20-dione.
A method of inducing anaesthesia which method comprises administering to a subject a composition as claimed in any one of claims 1 to 27 or 29, or a composition as claimed in claim 1 and prepared from a composition as claimed in any one of claims 16, 17 or 18, 18, 19 or 20.

DATED this 15th day of December, 1971.

GLAXO LABORATORIES LIMITED
By its Patent Attorneys:
CALLINAN AND NEWTON